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Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiological studies

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Abstract

Background: Recent pooled analyses support a beneficial impact of nut consumption on health, but whether nuts are associated with overall decreased mortality has not been yet reviewed.

Objective: We aimed to systematically review prospective studies exploring the effects of nut consumption on all-cause, cardiovascular disease (CVD), and cancer mortality and quantify the size effect through meta-analysis. We also reviewed confounding factors associated with nut consumption to assess potential clustering with other covariates.

Design: We searched PubMed and EMBASE for studies published up to June 2014. Study characteristics, hazard ratios (HRs) and 95% confidence intervals (CIs) were generated based on quantitative analyses. Dose-response analysis was performed when data were available.

Results: Seven studies for all-cause, six for CVD, and two for cancer mortality were included in this meta-analysis, with a total of 354,933 participants, 44,636 cumulative incident deaths and 3,746,534 cumulative person-years. Nut consumption was associated with some baseline characteristics, such as lower BMI and smoking status, as well as with increase intake of fruit, vegetable, and alcohol. One-serving of nuts per week and per day resulted in 4% (RR 0.96, 95% CI 0.93, 0.98) and 27% (RR 0.73, 95% CI 0.60, 0.88) decreased risk of all-cause mortality, respectively, and decreased risk of CVD mortality (RR: 0.93; 95% CI: 0.88, 0.99 and RR: 0.61; 95% CI: 0.42, 0.91, respectively). The effects were primarily driven by decreased coronary heart disease rather than stroke deaths. Nut consumption was also associated with a decreased risk of cancer death when comparing highest vs. lowest category of intake (RR: 0.86; 95% CI, 0.75, 0.98), but no dose-effect was found.

Conclusions: Nut consumption is associated with lower risk of all-cause, CVD, and cancer mortality, but presence of confounding factors should be taken into account when considering such findings.

Keywords: Nut consumption; mortality; prospective studies; cardiovascular diseases; cancer.

Introduction

Plant-based dietary patterns have been shown to have positive and significant impacts on human health over the last century (1). While most epidemiological studies have focused on fruits, vegetables, legumes, or cereals and morbidity/ mortality from chronic disease, a limited number of cohort studies have examined nut consumption and its potential beneficial effects on health outcomes (2). Nuts are a specific kind of fruit characterized by a hard shell and a dry seed rich in vitamins, phenolic compounds, fiber, and minerals, as well as high unsaturated fatty acid content relatively unique for fruits (3). Beneficial effects of nut consumption have been reported in relation to both cardiovascular disease (CVD) and cancer, although results on the latter are equivocal (2). Possible mechanisms of CVD risk reduction include anti-inflammatory, antioxidant, and anti-atherogenic properties of compounds such as tocopherols, folic acids, and phytochemicals that are common in nuts (3). Nut consumption has been demonstrated to have beneficial

effects on several cardiovascular risk factors, including lowering low-density lipoprotein cholesterol (LDL-c) (4), ameliorating endothelial function (5), decreasing visceral adiposity (6), improving hyperglycemia (7) and insulin resistance (8). Furthermore, nutrients contained in nuts may also modify specific processes related to cancer development, such as regulation of cell differentiation and proliferation, reduction of tumor initiation or promotion, DNA protection, and regulation of immunological and inflammatory responses (9).

Four recent meta-analyses demonstrated that higher consumption of nuts was associated with reduced risk of coronary artery disease and hypertension (10-13). However, pooled analyses exploring the effects of nut consumption on all-cause, CVD, and cancer mortality are lacking. Therefore, we aimed to systematically review prospective cohort studies investigating the association between nut consumption and mortality and review confounding factors associated with nut consumption to assess potential clustering with other covariates.

Methods

Study selection

A comprehensive search on MEDLINE and EMBASE databases of all English language studies on nut consumption and mortality published up to June 2014 was performed. Articles of potential interest were identified by using the search term “nut” combined with the terms: “mortality” or “survival”. Among the 240 articles retrieved, prospective cohort studies were identified and screened by reading the abstract and the full text when necessary. The reference lists of included manuscripts were also examined for any additional study not previously identified. The process of identification and inclusion of studies is summarized in **Figure 1**. Studies meeting the inclusion criteria: (i) evaluated the effects of nut consumption on the risk of mortality; (ii) assessed nut consumption by relative levels of intake (i.e., frequency or quantiles of consumption); and (iii) used a prospective cohort design. Exclusion criteria were: (i) studies reporting insufficient statistics or results; (ii) assessed nut consumption in combination with other food groups. If more than one article was published that used the same cohort, only the study including the entire cohort or with the longest follow-up was included.

Data extraction

Data were abstracted from each identified study by using a standardized extraction form. The following information was extracted from each study: i) name of the first author; ii) year of publication; iii) study cohort; iv) country; v) number of participants; vi) gender of participants; vii) age range of the study population at baseline; viii) follow-up period; ix) endpoints and cases; x) distributions of cases and person years, hazard ratios (HRs) and 95% confidence intervals (CIs) for all categories of exposure; xi) covariates used in adjustments; xii) background characteristics by categories of exposure. This process was independently performed by GG and SM; and any discordant entries were discussed and resolved by consensus.

The quality of each study was assessed according to Newcastle-Ottawa quality assessment Scale (14), consisting of three parameters of quality: selection (four points), comparability (two points), and outcome (three points); with a score of seven or more reflecting high quality. We also included the following additional criteria: completeness and accuracy of results (presence of person-years), ascertainment of exposure (nut consumption) with the outcomes of interest, number of participants (> 5000), duration of follow-up (>5 years), and adjustment for potential confounders (adequate vs. lacking of key confounders), for a total score of 14 points.

Statistical analysis

The outcomes evaluated in the analyses included all-cause, CVD, and cancer mortality. In the model evaluating CVD mortality, when a study evaluated specific CVD cause of death (i.e., coronary heart disease [CHD] or stroke), we included the most specific outcomes in order to control for possible differences across diseases.

HRs with 95% CIs for all categories of exposure were extracted for the analysis and random-effects models were used to calculate pooled relative risks (RRs) with 95% CIs for highest compared with lowest category of exposure and the dose-response analysis. Heterogeneity was assessed by using the Q test and I^2 statistic. The level of significance for the Q test was defined as $P < 0.10$. The I^2 statistic represents the amount of total variation that could be attributed to heterogeneity. I^2 values $\leq 25\%$, $\leq 50\%$, $\leq 75\%$ and $> 75\%$ indicated no, little, moderate, and significant heterogeneity, respectively. A sensitivity analysis excluding one study at a time was performed to assess the stability of results and potential sources of heterogeneity. A meta-regression analysis was conducted to test the effects on risk estimates as sources of heterogeneity of potential confounding factors considering year of publication, study quality, duration of follow-up, and amount of nut consumption in the highest category of exposure as moderators. We examined these hypothesized variables by fitting a mixed-effect model including such variables as moderators. To facilitate the interpretation of the effect of moderators, we obtained predicted average RRs by fitting four meta-regression models including each variable. Pooled effects were estimated via weighted least squares linear regression with natural logarithm of each study specific HR as dependent variable and with weights equal to the inverse of the sum of the within-study variance and the residual between-study variance. Publication bias was evaluated by visual investigation of funnel plots for potential asymmetry.

For dose-response analyses, the method reported by Greenland et al (15) and Orsini et al (16) was used to calculate study specific slopes ("corrected" linear trends) on the basis of results across categories of nut consumption. We extracted data on the amount of nut consumption, distributions of cases and person-years, and HRs with 95% CIs for ≥ 3 exposure categories. The median or mean weekly and daily amount of nut consumption in each category was assigned to the

corresponding HR with the 95% CI for each study. When nut consumption was reported by ranges of intakes, the midpoint of the range was used. When the highest category was open ended, we assumed the width of the category to be the same as the adjacent category. When the lowest category was open ended, we set the lower boundary to zero. Due to lack of person-years data in some studies, we additionally evaluated dose-response effect by calculating the "uncorrected" linear trend performing weighted least squares regression using HRs and CIs extracted for each intake category.

Background characteristics by category of exposure were graphically plotted to evaluate possible correlations. For each study, linear regression coefficients between nut consumption and alcohol, fruit, vegetable, and red meat intakes, as well as BMI and prevalence of smoking were estimated and subsequently meta-analyses to pool slope coefficients performed.

All analyses were performed in Review Manager (RevMan) version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) and R version 3.0.3 (Development Core Team, Vienna, Austria).

Results

Characteristics of included prospective studies

Eighteen out of the 25 originally selected studies were excluded after full-text examination for the following reasons: 1 study reported insufficient statistics; 1 study was conducted on subgroups of a cohort entirely evaluated in another study; 4 studies were conducted on same cohorts but with shorter follow-up periods; 12 studies explored the consumption of nuts grouped with other foods. Two additional studies meeting the inclusion criteria were identified by hand searching reference lists. This inclusion strategy resulted in the final selection of 9 studies (17-25) (Figure 1) with a total of 354,933 participants, 44,636 cumulative incident deaths and 3,746,534 cumulative person-years eligible to be included in the systematic review (**Table 1**). Geographically, these studies included 8 cohorts from the United States (US) (17-20, 23, 24), the Netherlands (21) and Spain (22, 25). Most of the studies examined individuals between the ages of 40 and 70. All studies included covariates that may have significant influence on mortality outcomes, such as age, gender (when not analyzed separately), body mass index (BMI), education, physical activity and smoking status. The covariates used for adjustments are described in Table 1. In general, study quality was good and comparable among different cohorts, despite one report (24) presented substantial limitations due to that it was published in the format of a conference abstract (see **Supplemental Table 1** under "Supplemental data" online). In addition, only 2 studies (19, 21) were conducted on general population.

Nut consumption and all-cause mortality

Six studies (18, 19, 22-25) were pooled together to estimate the risk of death in individuals with the highest intake of nuts compared to the lowest. The analysis

revealed an overall inverse association between higher nut consumption and all-cause mortality (RR 0.77, 95% CI 0.69, 0.87; **Figure 2**) with moderate evidence of heterogeneity ($I^2 = 56\%$). A sensitivity analysis was performed by exclusion of one study at a time and heterogeneity dropped to 49% when excluding Guasch-Ferré et al (22) which accounted for the highest weight (9.8%) amongst included studies. However, no substantial changes in the pooled risk estimate were found (RR: 0.80, 95% CI: 0.73, 0.89). The funnel plot suggested a publication bias against non-significant findings of benefit or harm associated with nuts or, analogously, toward findings with large effect sizes in favor of nuts (see **Supplemental Figure 1A** under “Supplemental data” online). After exclusion of these studies from the analysis, pooled RR still indicated a 20% decrease in all-cause mortality risk for highest category of nut consumption (RR: 0.80, 95% CI: 0.73, 0.89). Results of the meta-regression analysis showed none of the moderators examined had affected the analysis and therefore could potentially explain for the heterogeneity we observed (see **Supplemental Table 2** and **Supplemental Figure 2** under “Supplemental data” online).

Dose-response analysis exploring the effects of consuming 1-serving of nuts per week and per day was examined in 5 studies (19, 21-23, 25). We excluded studies that did not report detailed information on person-years (18, 24) and included Van den Brandt et al (21), which reported HRs for nut consumption frequency by treating it as a continuous variable. One-serving per week and per day resulted in 4% (RR: 0.96, 95% CI: 0.93, 0.98) and 27% (RR: 0.73, 95% CI: 0.60, 0.88) decreased risk of all-cause mortality, respectively (Figure 2). We observed moderate heterogeneity ($I^2 = 53\%$) and evidence of publication bias at funnel plot especially for 1-serving per week (see **Supplemental Figure 1B** and **Supplemental Figure 1C** under “Supplemental data” online). Heterogeneity and publication bias were due to the same aforementioned studies and their exclusion led to comparable but more consistent results ($I^2 = 0\%$) with no significant change in the final results (RR: 0.97, 95% CI: 0.96, 0.98 for 1-serving/week and RR: 0.81, 95% CI: 0.77, 0.86 for 1-serving/day). However, although the absolute difference in the RR estimates seem negligible, excluding two of the five studies causes a significant attenuation in the RR results of approximately 25% for weekly and 30% for daily consumption. Additional dose-response analysis that included all studies strengthened the effect size for both weekly (RR: 0.93, 95% CI: 0.90, 0.96) and daily (RR: 0.59, 95% CI: 0.48, 0.74) consumption of nuts on risk of all-cause mortality (see **Supplemental Figure 3** under “Supplemental data” online).

Nut consumption and CVD mortality

The association between nut consumption and CVD mortality was evaluated pooling data from 6 studies (17, 19, 20, 22-24) accounting for 7775 deaths from CVD. High consumption of nuts was inversely associated with CVD mortality risk compared to those with the lowest category of intake (RR: 0.71; 95% CI: 0.62, 0.81; **Figure 3**). We observed no significant evidence of heterogeneity

($I^2 = 25\%$) or publication bias (see **Supplemental Figure 4A** under “Supplemental data” online). After sensitivity analysis, no significant change of results was found. However, meta-regression analysis revealed a significant association with duration of follow-up as potential source of heterogeneity (see **Supplemental Table 2** and **Supplemental Figure 5** under “Supplemental data” online), as longer follow-up duration was associated with increased risk toward null effect.

Pooled RR to estimate HRs for 1-serving of nuts per week and per day was applied to 4 studies (19, 20, 22, 23) and resulted in decreased risks of CVD mortality (RR: 0.93; 95% CI: 0.88, 0.99 and RR: 0.61; 95% CI: 0.42, 0.91, respectively; Figure 3) with evidence of heterogeneity ($I^2 = 74\%$ and $I^2 = 75\%$, respectively) and publication bias on the funnel plot (see **Supplemental Figure 4B** and **Supplemental Figure 4C** under “Supplemental data” online). Evidence of publication bias may be attributed to studies exploring the association between nut consumption and death by stroke (23, 24). When excluded, the analysis resulted in decreased heterogeneity ($I^2 = 48\%$) and stable pooled risk. The subgroup analysis of studies evaluating mortality by specific CVD outcomes revealed that nut consumption was associated with significantly decreased risk of CHD death (RR: 0.70, 95% CI: 0.62, 0.79; $I^2 = 13\%$) and non-significant decrease in stroke mortality (RR: 0.84, 95% CI: 0.64, 1.09; $I^2 = 0\%$). The additional dose-response analysis, which included all studies, again strengthened the effect size for both weekly (RR: 0.90, 95% CI: 0.87, 0.92) and daily (RR: 0.48, 95% CI: 0.37, 0.63) consumption of nuts on CVD mortality risk (see **Supplemental Figure 6** under “Supplemental data” online).

Nut consumption and cancer mortality

Three studies (22-24) accounting for 10,423 deaths from cancer were included. There was a significant reduction of cancer mortality risk by nut consumption (highest vs. lowest category of exposure: RR: 0.86; 95% CI: 0.75, 0.98; **Figure 4**), with neither evidence of heterogeneity ($I^2 = 16\%$) nor publication bias (see **Supplemental Table 2**, **Supplemental Figure 7** and **Supplemental Figure 8** under “Supplemental data” online). Dose-response analysis was estimated pooling HRs of 2 studies (22-24) without significant results for both 1-serving of nuts per week and per day (Figure 4 and **Supplemental Figure 9** under “Supplemental data” online).

Background characteristics associated with nut consumption

Detailed information on subjects' background characteristics by nut consumption was reported in 5 studies (19, 20, 22, 23, 25). Pooled results of slope coefficient for meta-analysis of linear association between nut consumption and background characteristics revealed that each additional serving per week of nuts was associated with increased alcohol intake of about 1 gram per day (slope coefficient = 0.99, SE 0.79, 1.20), increased fruit intake of about 10 gram per day (slope coefficient = 9.82, SE 4.5, 15.14), increased vegetable

intake of about 13 gram per day (slope coefficient = 13.28, SE 6.09, 20.46), while BMI and smoking prevalence decreased by 0.15 kg/m² (slope coefficient = -0.15, SE -0.24, -0.06) and 0.59% (slope coefficient = -0.59, SE -0.99, -0.20), respectively (**Figure 5**). No association of nut consumption with red meat was found.

Discussion

This meta-analysis demonstrates consistent results among prospective cohort studies supporting decreased risks of mortality among individuals with higher nut intake. To the best of our knowledge, this is the first meta-analysis evaluating the effect of nut consumption on all-cause, CVD and cancer mortality.

While nut consumption and CVD morbidity outcomes have been thoroughly researched in the past, mortality risk is a relatively recent discussion among researchers. Indeed, the first publications demonstrating potential benefits of nut consumption on CVD mortality were conducted in the early '90s, such as the Adventist Health Study (17), the Iowa Women Health Study (19) and the Physicians Health Study (20). It was only during last few years that results from larger cohorts with more detailed information were published. The association was consistent for all-cause and CVD mortality, whereas the result was marginal for cancer mortality as only 3 studies examined this outcome (22-24). Although our results did not show a significant dose-response effect of nut consumption on cancer mortality, there were very limited studies available (two) to analyze limiting any conclusion.

Overall, the results from this analysis are convincing since a general agreement across studies included was observed in the pooled analysis. Recently published pooled analyses of prospective studies on nut consumption mostly focused on CVD-related morbidities, reporting a decreased risk of overall CVD, coronary heart disease (CHD), and hypertension (10-13). On the contrary, nut consumption was not observed to significantly decrease stroke incidence (10), which is in line with our results on association of stroke mortality.

Nuts are considered one of the most nutritional foods as they contain high amounts of vegetable protein and unsaturated fatty acids. Nuts have a wide variety of nutrients including dietary fiber, vitamins (folic acid, niacin, tocopherols, and vitamin B6), minerals (calcium, magnesium, potassium) and many other bioactive constituents such as phytosterols and phenolic compounds (26). The unique fat composition of nuts is characterized by low saturated fatty acid (SFA) content (4–16%) and high monounsaturated fatty acids (MUFA) content, such as oleic acid, as well as a variable amount of polyunsaturated fatty acids (PUFA), such as α -linolenic acid (ALA, the plant omega-3 fatty acid), which is especially abundant in walnuts (27). Among the other compounds that may exert a certain protection against CVD, nuts have high content of L-arginine, precursor of the endogenous vasodilator nitric oxide, which may contribute to vascular reactivity (28). Phytosterols may exert a cholesterol-lowering effect by reducing its absorption (29). Despite their high content of energy,

both epidemiological and experimental studies have reported that regular nut consumption does not contribute to obesity (30), nor does it increase the risk of developing metabolic syndrome (31). Their unique fatty acid composition is considered one of the key features responsible for nuts' health benefits of nuts, for instance in relation to their lipid-lowering and glucose metabolism ameliorating effects (4, 32). Among metabolic syndrome criteria, a meta-analysis of randomized controlled trials with dietary intervention based on nuts administration showed lowering in triglycerides and fasting plasma glucose compared with control diet interventions (33). There was no effect on waist circumference, high-density lipoprotein cholesterol or blood pressure, but the direction of effect favoring tree nuts for waist circumference was established (33). Additionally, another meta-analysis demonstrated that nuts improve glycemic control in individuals with type 2 diabetes, further supporting the inclusion of nuts in a healthy diet (34).

A number of studies have reported that nut consumption was associated with a decreased incidence of pancreatic (35) and colorectal cancer (36, 37), whereas some case-control studies reported a decreased association with endometrial (38) and prostate cancer (39), suggesting a logical substrate for the marginally significant decreased risk of cancer mortality observed in this study. It is hypothesized that nuts provide beneficial protection against cancer through their anti-oxidant and anti-inflammatory properties, for instance, by reducing lipid peroxidation or oxidative DNA damage (40). Fiber and folate in nuts may also play a role in cancer mortality prevention. Fiber decreases intestinal mucosa's exposure to carcinogens by increasing anaerobic fermentation and reducing intestinal transit duration (31). Folate, a B-vitamin necessary for normal cellular function, DNA synthesis and metabolism, may reduce DNA damage or induce repair, and it is thought to play an important role in detoxifying homocysteine (41). Although experimental studies suggest that nuts may have chemopreventive action, especially on colorectal and prostate cancer (40), no sufficient evidence confirming their anticancer properties is currently available. Further research is needed to better understand the potential mechanisms through which nuts may decrease cancer risks.

Potential limitations of the studies included in this meta-analysis include possible residual confounding effect by variables not equally distributed among categories of exposure. To further evaluate findings, it is important to consider adjustments for potential confounders. Five studies (19, 20, 22, 23, 25) included in this meta-analysis reported distribution of baseline characteristics of participants studied. After pooling together data for characteristics that potentially play a role in mortality, we reported that nut consumption was associated with lower BMI and decreased smoking status. In Bao et al. (23), a specific analysis for each potential confounding factor was performed to demonstrate that inverse association between nut consumption and mortality persisted across subgroups, but no further analyses could be retrieved from other studies. Similarly, all investigations agreed that nut consumption was correlated with fruit, vegetable, and alcohol intakes. Although we have limited

information on participants' background characteristics from other cohorts, our analyses on studies with sufficient data indicate that higher nut consumption was positively correlated with healthier background characteristics. It is unclear if the protective effects we observed are mediated by nut consumption or through the clustering healthy food preferences. Nonetheless, nut consumption may reflect overall healthier lifestyle choices that eventually lead to decreased mortality risk.

Our study also has some specific limitations. First, cancer mortality was assessed only in 3 out of the 9 cohorts investigated. Besides the lower statistical power compared with other analyses, it is also possible that results from other cohorts on nut consumption and cancer mortality were not significant and unpublished. Second, our analysis indicated an association between nut consumption and mortality, but whether or not the relationship is independent of other dietary and/or lifestyle factors remains unknown. Thus, as suggested above, higher nut consumption may be part of better nutrition and lifestyle habits that all contributed to decreased mortality. Third, questions about specific consumption over time, duration, and type of nuts in relation with mortality remain to be elucidated. Fourth, most of the studies included were conducted on specific group of individuals with social (i.e., healthcare workers (20, 23), post-graduate students (25)) or health-related (i.e., individuals at high CVD risk (22)) characteristics that differ them from general population. Thus, findings from such cohorts may not be universally generalizable.

In conclusion, nut consumption was inversely associated with all-cause, CVD and, cancer mortality. Future research should emphasize exploring more detailed background characteristics of the study population in order to better isolate the independent effects of nut consumption from overall dietary patterns, lifestyle habits and mortality. Moreover, more information on the specific type of nuts consumed would be of interest in order to better identify specific constituents responsible for their health benefits.

Acknowledgments

Author contributions were the following: GG designed research; GG and SM conducted research; GG, SM, and AM analyzed data; GG, JY and SNK wrote the paper; GG, FG, and SNK had primary responsibility for final content. All authors declare no conflicts of interest.

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Table 1. Identified prospective cohort studies evaluating nut consumption and all-cause, stroke and cardiovascular (including ischemic coronary disease [ICD], coronary heart disease [CHD] and cardiovascular disease [CVD]) mortality.

Author, year	Cohort (country)	Gender	Age range	No. of subjects	Outcome	Follow-up	No. of cases	Person-years	Adjustments	Study quality
Frasier, 1992 (17)	Adventists Health Study, non-hispanic white (US)	Men and Women	25+	26,473	ICD mortality	6 y	463	158,838	Age, gender, smoking status, physical activity, relative weight, and high blood pressure.	11
Frasier, 1997 (18)	Adventists Health Study, black (US)	Men and Women	25+	1668	All-cause mortality	10 y	153	15,893	Age, smoking status, physical activity.	10
Ellsworth, 2001 (19)	Iowa Women's Health Study (US)	Women	55-69	41,836	All-cause mortality, CHD mortality	10 y	3726	387,991	Age, energy intake, BMI, waist-to-hip ratio, alcohol consumption, smoking status, history of diabetes, history of hypertension, history of estrogen use, physical activity, education, consumption of cereal fibre, eggs, green leafy vegetables, red meat, whole grain foods, and Keys dietary lipid score.	14
Albert, 2002 (20)	Physicians' Health Study (US)	Men	40-84	22,071	CHD mortality	17 y	566	366,751	Age, aspirin and beta carotene treatment assignment, evidence of CVD before 12-month questionnaire, BMI, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, vigorous exercise, vitamin E, vitamin C, multivitamin use at baseline, fish consumption, and red meat, fruit, vegetable, and dairy intake at 12 months of follow-up.	13
Van den Brandt, 2011 (21)	Netherlands Cohort Study (Netherlands)	Men and Women	55-69	120,852	All-cause mortality	10 y	9691	33,872	Age, cigarette smoking status, number of cigarettes smoked per day, years of smoking, BMI, hypertension, highest level of education, and energy intake.	12
Guasch-Ferré, 2013 (22)	PREDIMED Study (Spain)	Men and Women	55-80	7216	All-cause mortality, CVD mortality, cancer mortality	4.8 y	323	31,077	Age, gender, intervention group, BMI, smoking status, educational level, leisure time physical activity, history of diabetes, history of hypercholesterolemia, use of oral antidiabetic medication, use of antihypertensive medication, use of statins, total energy intake, consumption of vegetables, fruits, red meat, eggs, and fish, alcohol intake, and Mediterranean diet adherence.	13

Bao, 2013 (23)	Nurses' Health Study (US)	Women	30-55	76,464	All-cause mortality, CVD mortality, cancer mortality	30 y	16,200	3,038,853	Age, race, BMI, level of physical activity, status with regard to smoking, whether a physical examination was performed for screening purposes, current multivitamin use, and current aspirin use, status with regard to a family history of diabetes mellitus, myocardial infarction, or cancer, status with regard to a history of diabetes mellitus, hypertension, or hypercholesterolemia, intake of total energy, alcohol, red or processed meat, fruits, and vegetables, menopausal status and hormone use.	13
Bao, 2013 (23)	Health Professional Follow-up Study (US)	Men	40-75	42,498	All-cause mortality, CVD mortality, cancer mortality	24 y	11,229		Age, race, body-mass index, level of physical activity, status with regard to smoking, whether a physical examination was performed for screening purposes, current multivitamin use, and current aspirin use, status with regard to a family history of diabetes mellitus, myocardial infarction, or cancer, status with regard to a history of diabetes mellitus, hypertension, or hypercholesterolemia, intake of total energy, alcohol, red or processed meat, fruits, and vegetables.	13
Djousse, 2014 (24)	Physicians' Health Study (US)	Men	40-84	20,742	All-cause mortality, CVD mortality, cancer mortality	9.5 y	2,732		Age, BMI, alcohol use, smoking, exercise, energy intake, saturated fat, fruit and vegetables, red meat intake, and prevalent diabetes and hypertension.	12
Fernandez-Montero, 2014 (25)	SUN Cohort Study	Men and Women	18+	17,184	All-cause mortality	5 y	119	80,010	Age, gender, BMI, smoking, alcohol intake, adherence to the Mediterranean diet, use of special diets, marital status, baseline hypercholesterolemia, hypertension, physical activity, length of television watching, baseline presence of cancer, cardiovascular disease, or diabetes.	13

CHD, coronary heart disease; CVD, cardiovascular disease; ICD, ischemic coronary disease; PREDIMED, PREvencion con DIeta MEDiterranea; SUN, Seguimiento University of Navarra.

Figure 1. Screening and selection process utilized in this systemic review to include studies that evaluated nut consumption and mortality risk.

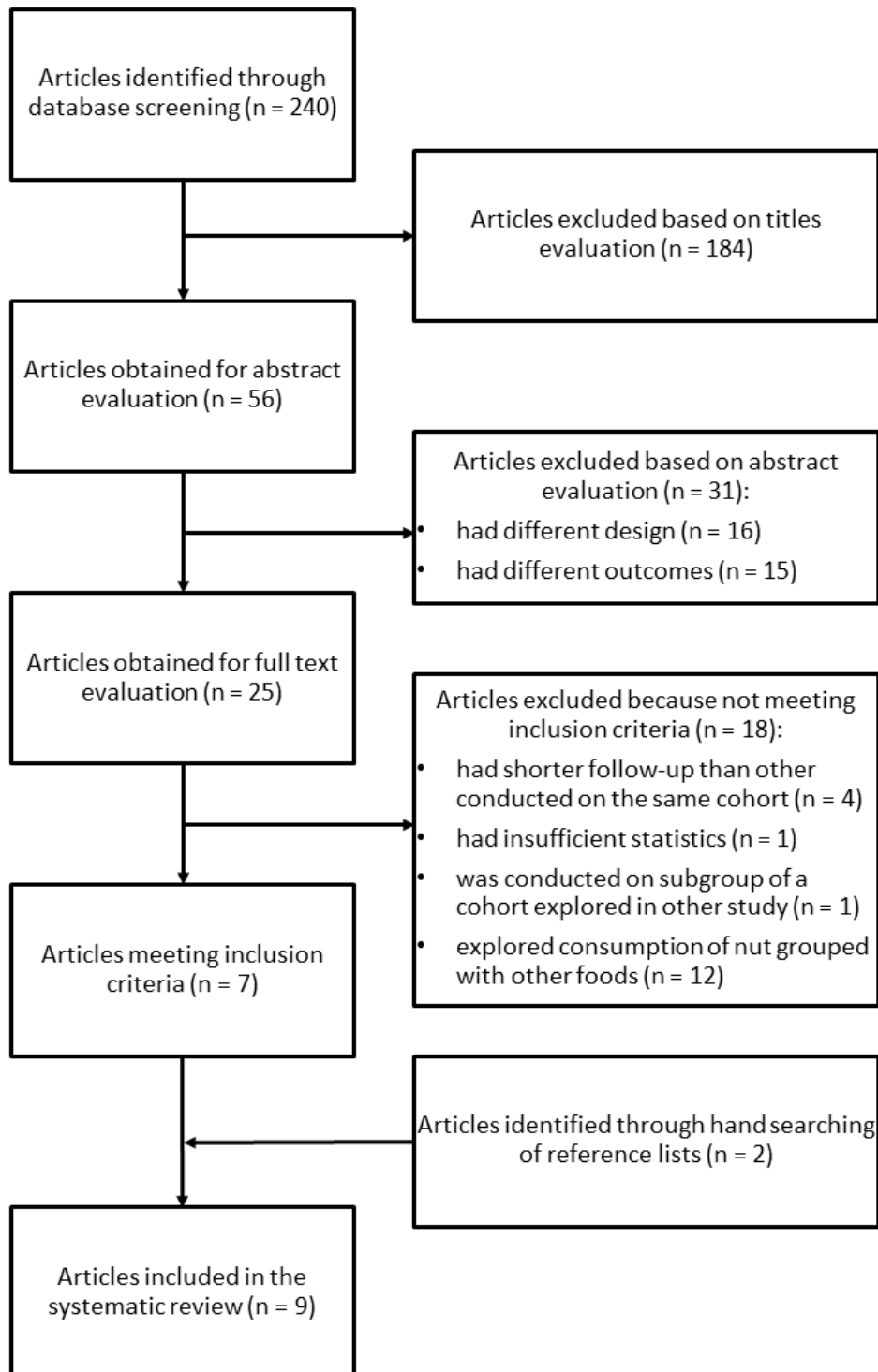


Figure 2. Forest plot evaluating pooled risk ratios (RRs) of all-cause mortality by nut consumption. Size of the squares is proportional to the percentage weight of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95% CIs of risk assessed by considering nut consumption as category of exposure (highest vs. lowest category of consumption) or by dose-response analysis (daily and weekly intake of 1 serving, equivalent to 28 grams) through “corrected” linear trends.

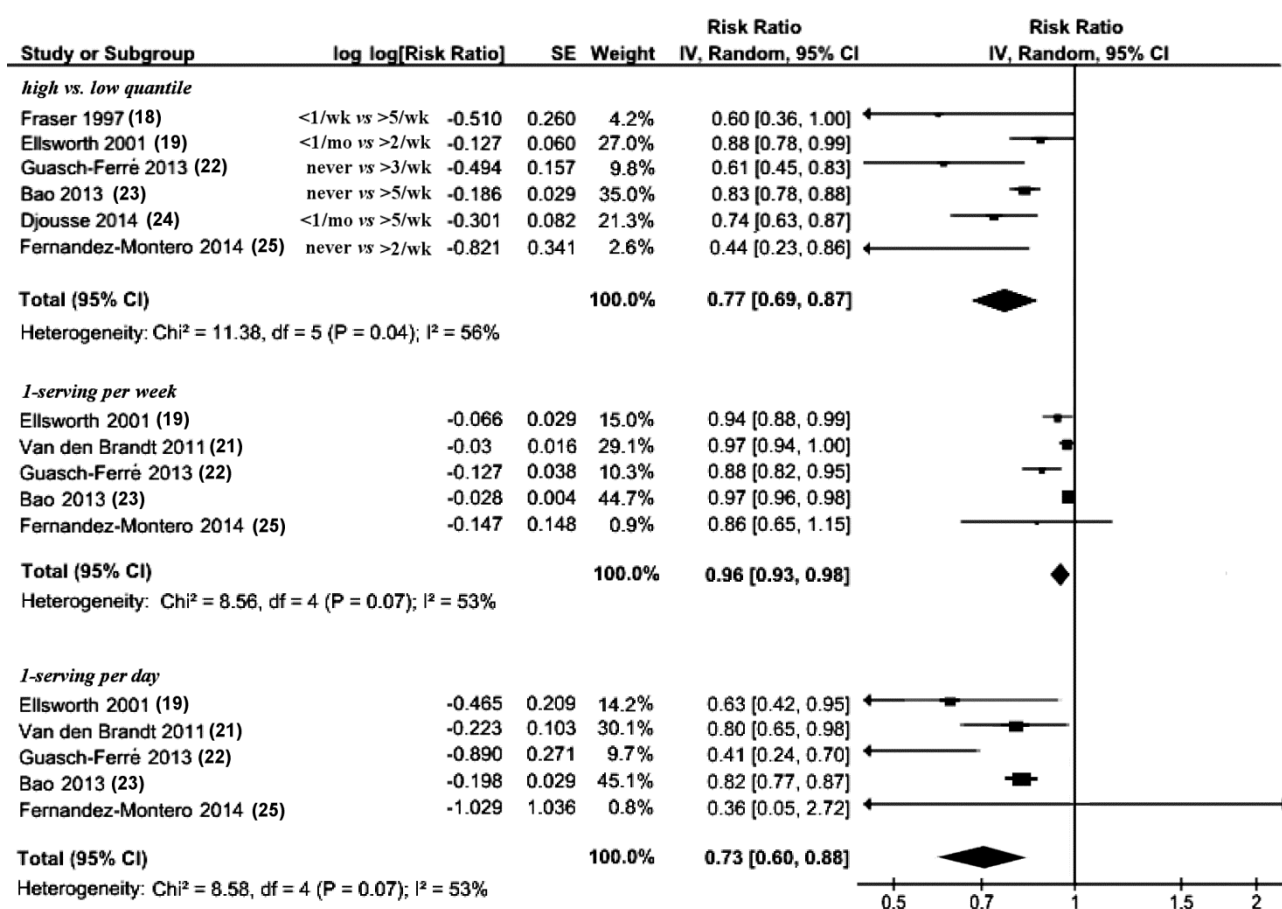


Figure 3. Forest plot evaluating pooled risk ratios (RRs) of cardiovascular mortality (including coronary heart disease and stroke mortality) by nut consumption. Size of the squares is proportional to the percentage weight of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95% CIs of risk assessed by considering nut consumption as category of exposure (highest vs. lowest category of consumption) or by dose-response analysis (daily and weekly intake of 1 serving, equivalent to 28 grams) through “corrected” linear trends. CHD, coronary heart disease; n.s., not specified.

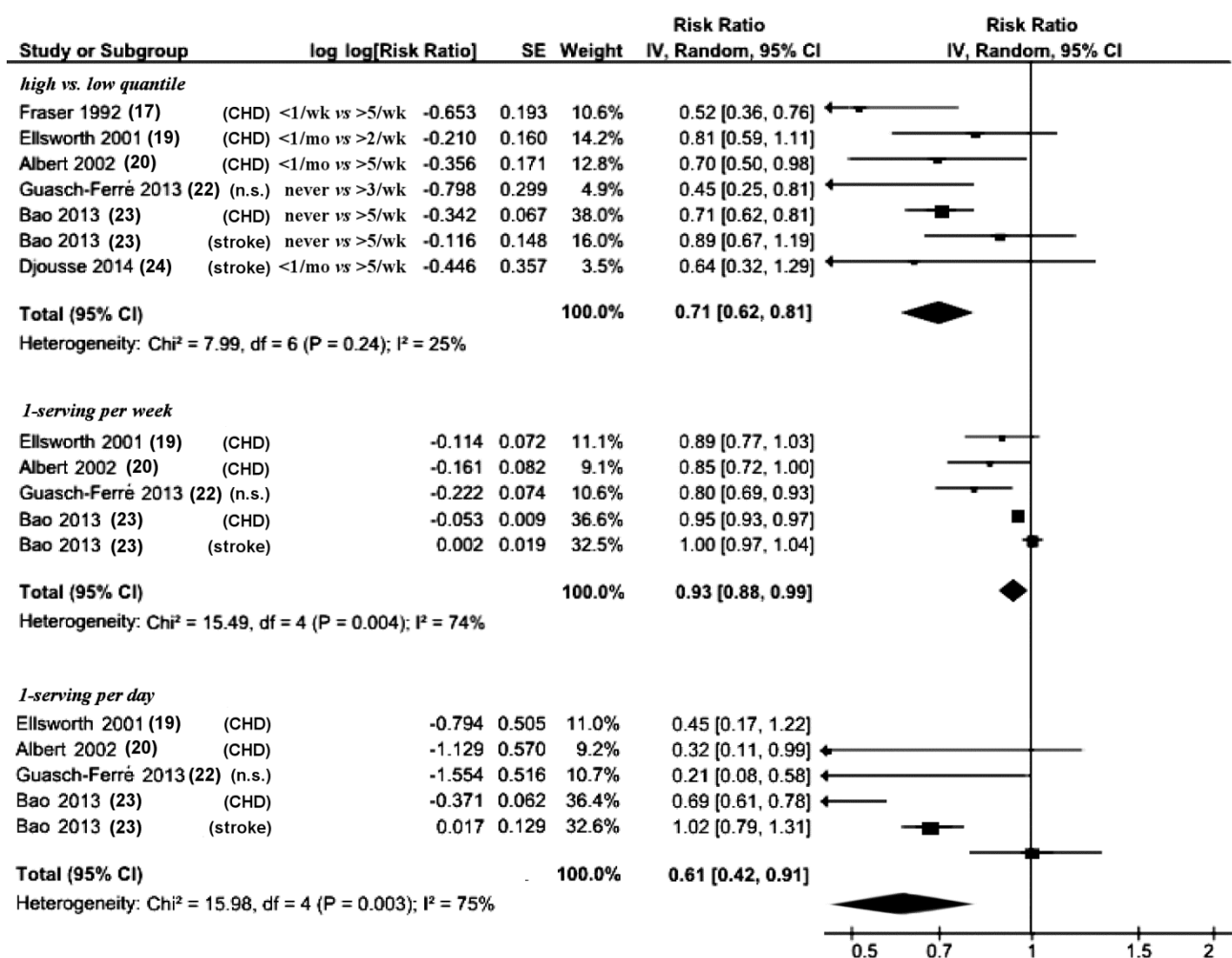


Figure 4. Forest plot evaluating pooled risk ratios (RRs) of cancer mortality by nut consumption. Size of the squares is proportional to the percentage weight of each study; horizontal line represents 95% confidence intervals (CI); diamonds represent pooled estimates and 95% CIs of risk assessed by considering nut consumption as category of exposure (highest vs. lowest category of consumption) or by dose-response analysis (daily and weekly intake of 1 serving, equivalent to 28 grams) through “corrected” linear trends.

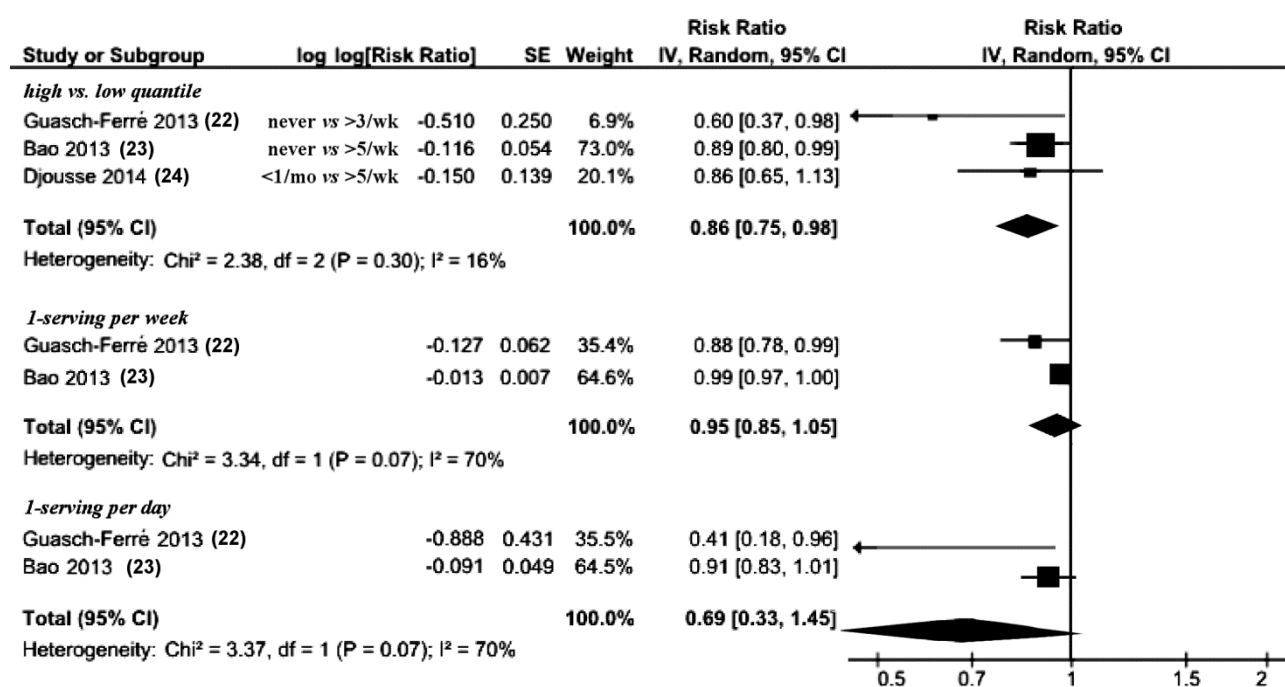


Figure 5. Scatter plot for associations between nut consumption and background characteristics including: A) alcohol intake, B) fruit intake, C) vegetable intake, D) red meat intake, E) BMI, and F) percentage of smokers. Light lines represent linear regression coefficients of individual studies; bold lines represent pooled estimates average increase of each variable per increase of nut intake.

